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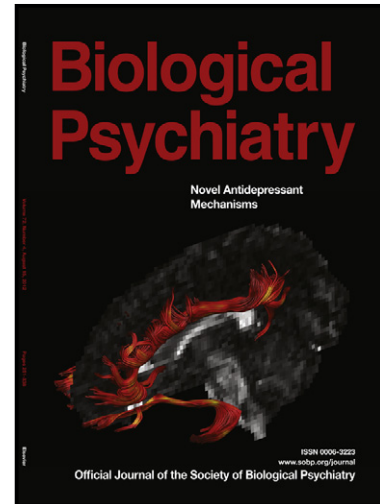
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Intranasal oxytocin: a reply to Quintana and Woolley

Gareth Leng and Mike Ludwig

Centre for Integrative Physiology, University of Edinburgh, EH9 8XD UK

Corresponding author: Gareth Leng

Gareth Leng

Professor of Experimental Physiology

Centre for Integrative Physiology

University of Edinburgh

Hugh Robson Bldg, George Square

Edinburgh EH8 9XD, UK

Tel: +44 (0) 131 650 2869

Fax: +44 (0) 131 650 3711

Email: Gareth.Leng@ed.ac.uk

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We are very pleased that Quintana and Woolley (1) have engaged with the issues raised in our review (2); we believe that the field is best advanced by frank exchanges that identify issues of concern and ways to resolve them. We address the points raised in the order that they raise them.

Quintana and Woolley cite three meta-analyses as supporting the ability of intranasal oxytocin to alter cognition. While we had suggested the possibility of publication bias in the literature on intranasal oxytocin (reflecting widespread concern about publication bias in both clinical and biological research), these meta-analyses indeed reported no evidence for this. However, Walum et al. (3) recently re-analysed the studies covered by these meta-analyses. They concluded that the studies were seriously underpowered, and argue that this is true generally of studies with intranasal oxytocin. Given such low power, they argue that ~80% of attempts to replicate any given study should fail to achieve statistical significance. They conclude that the relative absence of negative findings in the literature suggests that *either* publication bias is present, *or* that the excess of positive findings results from questionable research practices.

Quintana and Woolley were surprised that we cited one of their studies (4) as evidence that intranasal oxytocin has no effect on patients with schizophrenia or healthy volunteers. We should not have cited that study so simplistically, and apologise. In that study, Woolley et al.

gave oxytocin intranasally to schizophrenic patients and healthy controls, and tested them with the Reading the Mind in the Eyes Test (RMET) and The Awareness of Social Inference Test (TASIT). They found no significant effect on either test in healthy volunteers, and no effect on the RMET in schizophrenic patients. The TASIT test has three parts; they found an effect only in the third part, which addresses ‘controlled social cognition’ rather than the ‘automatic social cognition assessed by other test elements. Their failure to find an effect on automatic social cognition was a primary outcome, as previous studies had reported effects on automatic processes, but we should not have neglected their positive finding. Quintana and Woolley state that this has been reported independently by other groups, citing Davis et al (5), who also used the third part of TASIT. However, Davis et al. found no significant effect of oxytocin on this or indeed on any of the three other tests that they used. Only when they combined one sub-element of the third domain of TASIT (sarcasm scores) with results from one of the other tests did they find a marginally significant effect.

Although Woolley et al. (4) found no overall effect of oxytocin with RMET in healthy volunteers, in a post-hoc analysis they found an effect on the harder test items, partially replicating previous findings. For this, they selected test items which had attracted the lowest scores in the placebo condition, and compared the scores in the oxytocin condition. However, chance effects alone should produce a higher score for the ‘harder’ items identified in this way (‘regression to the mean’). Equally, chance effects should produce a lower score for the ‘easier’ items – and from the Supplementary Material that they provided, this appears indeed to be the case.

Quintana and Woolley argue that, although intranasal oxytocin produces only modest rises in CSF, these may still be functionally relevant. As detailed in our review, in animal studies, behavioural effects of intracerebroventricular oxytocin are only seen with injections that achieve very high CSF concentrations. In the only study measuring oxytocin in human CSF after intranasal application Striepens et al. (6) found no increase after 45 or 60min, and only a modest (64%) increase after 75min, using a dose of 24 IU (6). As Quintana and Woolley argue that a much lower dose (8IU) may be more efficacious than 24IU, and as virtually all studies have tested subjects in a time window where Striepens et al. found no increase, we find it hard to see their case that CSF levels are relevant for the apparent effects of intranasal oxytocin.

In our review, we drew attention to the critical step of sample extraction when quantifying plasma oxytocin; measures of oxytocin in unextracted samples are much higher than, and do not correlate with, measures in extracted samples, and they appear not to reflect biologically active oxytocin. As Quintana and Woolley point out, this is not relevant to the issue of the effectiveness of intranasal oxytocin. However, these issues have become deeply entangled; for example, Woolley et al. (4) cite two studies of plasma oxytocin in their study rationale, both of which used the controversial assay of unextracted plasma.

We congratulate Quintana et al. (7) for, for the first time in studies of intranasal oxytocin, including a group given oxytocin intravenously, and hope that this important control will become routine. Their study, involving recognition of facial emotions, used two doses of intranasal oxytocin (8IU and 24IU). There were no effects of either dose on happy ratings of ambiguous faces, angry or happy ratings of angry faces, or angry or happy ratings of happy faces. There was an apparent effect only on angry ratings of ambiguous faces, and only at the lower dose. This effect was significant on pairwise comparisons against both the placebo and the higher dose of intranasal oxytocin, but, importantly, not against i.v. oxytocin.

We appreciate the importance of effective therapies for impaired social cognition, and the evidence from animal studies makes the central oxytocin systems a key target. At present, we believe that there are no robustly replicable measures of the effectiveness of intranasal oxytocin on social cognition, no understanding of its mechanism of action, and no certainty that effects are mediated by actions in the brain.

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References

1. Quintana DS, Woolley JD (2015): Intranasal oxytocin mechanisms can be better understood but its effects on social cognition and behavior are not to be sniffed at. *Biol Psychiatry*.
2. Leng G, Ludwig M (2015): Intranasal oxytocin: myths and delusions. *Biol Psychiatry*.
3. Walum H, Young LJ (2015): Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. *Biol Psychiatry*. (in press).
4. Woolley J, Chuang B, Lam O, Lai W, O'Donovan A, Rankin K, et al. (2014): Oxytocin administration enhances controlled social cognition in patients with schizophrenia. *Psychoneuroendocrinology* 47:116-125.
5. Davis MC, Lee J, Horan WP, Clarke AD, McGee MR, Green MF, et al. (2013): Effects of single dose intranasal oxytocin on social cognition in schizophrenia. *Schizophr Res* 147:393-397.
6. Striepens N, Kendrick KM, Hanking V, Landgraf R, Wüllner U, Maier W, Hurlmann R. (2013) Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. *Sci Rep* 3:3440.
7. Quintana DS, Westlye, L.T., Rustan, Ø.G., Tesli, N., Poppy, C.L., Smevik, H., Tesli, M., Røine, M., Mahmoud, R.A., Smerud, K., Djupesland, P.G., Andreassen, O.A. (2015): Low dose oxytocin delivered intranasally with Breath Powered device affects social-cognitive behavior: a randomized 4-way crossover trial with nasal cavity dimension assessment. *Transl Psychiatry*. (in press).